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UNITED STATES ARMY ENVIRONMENTAL HYGIENE AGENCY

ABERDEEN PROVING GROUND, MD 21010-5422

TOPICAL HAZARD EVALUATION PROGRAM
OF
CANDIDATE INSECT REPELLENTS AI3-39013a,
AI3-6605, AI3-38303b
US DEPARTMENT OF AGRICULTURE PROPRIETARY CHEMICALS
STUDY NOS. 75-51-0482-86, 75-51-0507-86, 75-51-0536-86
AUGUST 1986

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Maurice H. Weeks

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U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010-6422

REPLY TO ATTENTION OF
HSHB-MO-T

30 September 1986

SUBJECT: Topical Hazard Evaluation Program of Candidate Insect Repellents, AI3-39013a, AI3-6605, and AI3-38303b, US Department of Agriculture Proprietary Chemicals, Study Nos. 75-51-0482-86, 75-51-0507-86, 75-51-0536-86, August 1986

Executive Director
Armed Forces Pest Management Board
Forest Glen Section, WRAMC
Washington, DC 20307-5001

EXECUTIVE SUMMARY

The purpose and recommendations of the enclosed report follow:

a. Purpose. The purpose of this program is to provide guidance for further entomological testing of the Candidate Insect Repellents AI3-39013a, AI3-6605, and AI3-38303b by means of laboratory animal studies using Sprague-Dawley rats, New Zealand white rabbits, and Albino-Hartley guinea pigs.

b. Recommendations. ~~Recommend~~ chemicals AI3-6605 and AI3-38303b be disapproved for further entomological testing. If efficacy data is felt to warrant further entomological studies of any chemical, it should be resubmitted in a further purified form or at the intended use concentration. Further recommend that chemical AI3-39013a be approved for further entomological testing with the warning that this chemical should be used with caution around the eyes and mucosa.

FOR THE COMMANDER:

Encl

N. JOE THOMPSON
Colonel, MC
Director, Occupational and
Environmental Health

CF:
HQDA(DASG-PSP-E) (wo/encl)
Dir, Advisory Cen on TOX, NRC (2 cy) (w/encl)
Comdt, AHS (HSHA IPM) (w/encl)
USDA, ARS (Dr. Terrence McGovern)
USDA, ARS-Southern Region (3 cy) (w/encl)
USDA, ARS-Southern Region (COL Moussa) (w/encl)
Cdr, USAMRDC (SGRD-DPM) (COL Reinert) (w/encl)

DEPARTMENT OF THE ARMY
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010-5422

REPLY TO ATTENTION OF

HSHB-MO-T

TOPICAL HAZARD EVALUATION PROGRAM
OF
CANDIDATE INSECT REPELLENTS AI3-39013a,
AI3-6605, AI3-38303b
US DEPARTMENT OF AGRICULTURE PROPRIETARY CHEMICALS
STUDY NOS. 75-51-0482-86, 75-51-0507-86, 75-51-0536-86
AUGUST 1986

1. AUTHORITY.

a. Letter, US Department of Agriculture-Agricultural Research Service, Northeastern Region, Beltsville Agricultural Research Service, Beltsville, Maryland, 6 December 1983.

b. Letter, US Department of Agriculture-Agricultural Research Service, Northeastern Region, Beltsville Agricultural Research Service, Beltsville, Maryland, 31 May 1984.

c. Letter, US Department of Agriculture-Agricultural Research Service, Northeastern Region, Beltsville Agricultural Research Service, Beltsville, Maryland, 26 November 1984.

d. Memorandum of Understanding between the US Army Environmental Hygiene Agency; the US Army Health Services Command; the Department of The Army, Office of The Surgeon General; the Armed Forces Pest Control Board; and the US Department of Agriculture, Agricultural Research, Science and Education Administration; titled, Coordination of Biological and Toxicological Testing of Pesticides, effective 23 January 1979.

2. REFERENCES.

a. Toxicology Division Standing Operating Procedures, US Army Environmental Hygiene Agency (USAEHA), 1982.

b. Toxicology Division, Topical Hazard Evaluation Program Procedural Guide, October 1985.

c. Gleason et. al., "Clinical Toxicology of Commercial Products," Williams and Wilkins, Baltimore, Maryland, 1969.

d. "Mutagenicity Evaluation of AI3-39013a, D6217 in the Ames Salmonella/Microsome Reverse Mutation Assay," Hazleton Biotechnologies Co., 5516 Nicholson Lane, Kensington, MD 20895, July 1986.

3. PURPOSE. The purpose of this program is to provide guidance for further entomological testing of the Candidate Insect Repellents AI3-39013a, AI3-6605, and AI3-38303b US Department of Agriculture (USDA) Proprietary Chemicals.

4. MATERIALS AND METHODS.*†

a. Testing for primary skin irritation, photochemical skin irritation, and primary eye irritation was conducted using New Zealand white rabbits from either Hazleton-Dutchland Laboratories, Denver, Pennsylvania or Buckshire Farms, Perkasie, Pennsylvania. Albino-Hartley guinea pigs from Hazleton-Dutchland Laboratories, Denver, Pennsylvania were used for sensitization studies, and Sprague-Dawley rats from Charles River Laboratories, Wilmington, Massachusetts were used for determination of Approximate Lethal Doses (ALD's).

b. All samples tested in these studies were synthesized by Dr. Terrence P. McGovern, Organic Chemical Synthesis Laboratory, USDA, Beltsville, Maryland.

c. Primary skin and eye irritation studies were performed as described in reference 2b on all subject chemicals. Photochemical irritation studies and determination of ALD were performed (reference 2b) on chemicals AI3-39013a, and AI3-6605. Guinea Pig Sensitization Testing (reference 2b, Modified Landsteiner Technique) was performed on chemical AI3-39013a. An in vitro study (Ames Test) of chemical AI3-39013a was performed under contract DAAD05-86-M-L723 (reference 2c).

5. RESULTS.

a. AI3-39013a. Chemical AI3-39013a produced no primary irritation (Appendix A, Category I) of intact or abraded rabbit skin and produced mild corneal and conjunctival injury (Appendix A, Category C) to rabbit eyes. During the primary eye irritation test, one of nine test animals exhibited lesions persisting at 7 days post application. Due to the mildness of lesions in the other eight test animals, it is reasonable to suspect that the one more seriously affected animal may have had a predisposition or complicating condition. This chemical was neither a sensitizer nor a photochemical irritant within the limits of our tests and was moderately toxic (reference 2c) by the oral route in male rats (ALD = 2278 mg/kg).

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* In conducting the studies described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," US Department of Health, Education and Welfare Publication No. (NIH) 85-23, 1985.

† The studies reported herein were performed in animal facilities fully accredited by the American Association for the Accreditation of Laboratory Animal Care.

Rats which died after oral dosing with AI3-39013a showed salivation, intestines distended with fluid, and full urinary bladders. One rat showed pulmonary edema, congested adrenal glands, and scattered hemorrhagic areas. All dosed rats showed a dose dependent depression and ataxia. In the Ames Salmonella/Microsome Plate Test (reference 2i) chemical AI3-39013a was not mutagenic either in the presence or absence of metabolic activators.

b. AI3-6605. Chemical AI3-6605 produced mild irritation to the intact and abraded skin of rabbits (Appendix A, category II); a light scaliness was noted on application sites. Two animals showed small scabs at the application sites, however, due to the lack of erythema and edema it is not clear that this was induced by the chemical. Caution should be exercised should this chemical ever be tested further. AI3-6605 was not a photo-irritant within the limits of our test but caused severe injury to the cornea and conjunctiva (Appendix A, category F) of rabbit eyes as well as a marked iritis. The ALD in male rats by the oral route was >5,000 mg/kg. Per reference 2c, this compound would be considered slightly toxic under the test conditions.

c. AI3-38303b. Chemical AI3-38303b produced mild primary irritation of intact and abraded rabbit skin (Appendix A, category II) and produced moderate to severe injury to the cornea and conjunctiva of rabbit eyes (Appendix A, category E). Eye lesions persisted at seven days post application and consisted of corneal opacity (some areas of which still took a flourescein stain) and mild perilimbal vascularization. Several animals exhibited a transient iritis.

6. RECOMMENDATIONS.

a. Recommend chemicals AI3-6605 and AI3-38303b be disapproved for further entomological studies. If efficacy data for any of these chemicals warrant further study, that chemical should be resubmitted in a further purified form or at the intended use concentration.

b. Recommend that chemical AI3-39013a be approved for further entomological testing. This chemical should be used with caution around the eyes and mucosa.

7. ACKNOWLEDGEMENT. This Topical Hazard Evaluation Study was conducted by CPT R. David Russell, who has since departed this Agency.

Maurice H. Weeks

MAURICE H. WEEKS
Chief, Toxicology Division

APPENDIX A

TOPICAL HAZARD EVALUATION PROGRAM DEFINITIONS OF CATEGORIES OF COMPOUNDS BEING CONSIDERED FOR ACUTE SKIN APPLICATION

CATEGORY I - Compounds producing no primary irritation of the intact skin or no greater than mild primary irritation of the skin surrounding an abrasion. (INTERPRETATION: No restriction for acute application to the human skin.)

CATEGORY II - Compounds producing mild primary irritation of the intact skin and the skin surrounding an abrasion. (INTERPRETATION: Should be used only on human skin found by examination to have no abrasions or may be used as a clothing impregnant.)

CATEGORY III - Compounds producing moderate primary irritation of the intact skin and the skin surrounding an abrasion. (INTERPRETATION: Should not be used directly on the skin without a prophetic patch test having been conducted on humans to determine irritation potential to human skin. May be used without patch testing, with extreme caution, as clothing impregnants. Compound should be resubmitted in the form and at the intended use concentration so that its irritation potential can be reexamined using other test techniques on animals.)

CATEGORY IV - Compounds producing moderate to severe primary irritation of the intact skin and of the skin surrounding an abrasion. (INTERPRETATION: Should be resubmitted for testing in the form and at the intended use concentration. Upon resubmission, its irritation potential will be reexamined using other test techniques on animals, prior to possible prophetic patch testing in humans, at concentrations which have been shown not to produce primary irritation in animals.)

CATEGORY V - Compounds impossible to classify because of staining of the skin or other masking effects owing to physical properties of the compound or compounds producing necrosis, vesiculation, or eschars. (INTERPRETATION: Not suitable for use on humans.)

EYE CATEGORIES:

A. Compounds noninjurious to the eye. INTERPRETATION: Irritation of human eyes is not expected if the compound should accidentally get into the eyes, provided it is washed out as soon as possible.

B. Compounds producing mild injury to the cornea. INTERPRETATION: Should be used with caution around the eyes.

C. Compounds producing mild injury to the cornea, and in addition some injury to the conjunctiva. INTERPRETATION: Should be used with caution around the eyes and mucosa (e.g., nose and mouth).

D. Compounds producing moderate injury to the cornea. INTERPRETATION: Should be used with extreme caution around the eyes.

E. Compounds producing moderate injury to the cornea, and in addition producing some injury to the conjunctiva. INTERPRETATION: Should be used with extreme caution around the eyes and mucosa.

F. Compounds producing severe injury to the cornea and to the conjunctiva. INTERPRETATION: Should be used with extreme caution. It is recommended that use be restricted to areas other than the face.

APPENDIX B

ANALYTICAL QUALITY ASSURANCE

The Analytical Quality Assurance Office certifies the following with regard to this study:

a. This study was conducted in accordance with:

(1) Standing Operating Procedures developed by the Toxicology Division, USAEHA.

(2) Title 21, Code of Federal Regulations (CFR), 1985 rev, Part 58, Good Laboratory Practice for Nonclinical Laboratory Studies.

b. Facilities were inspected during its operational phase to ensure compliance with paragraph a above.

c. The information presented in this report accurately reflects the raw data generated during the course of conducting the study.

Timothy L. Fisher

TIMOTHY L. FISHER
Chief, Analytical Quality
Assurance Office